12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

The designated wound sites received a single application of the control dressing or the investigational dressing. Wounds assigned to the control dressing received Biobrane-L coverage. Removal of the outer dressing layers on the Biobrane-L site was generally performed after the initial 24-48 hours following surgery. The timing of Biobrane-L removal was expected to be variable from patient to patient, however attempts to peel Biobrane-L from newly formed epidermis generally began between the 7^{th} and 10^{th} post operative days. Those areas where Biobrane-L separated easily from the underlying donor surface were trimmed back. Those areas where Biobrane-L remained adherent to the test site despite soaking were considered non-epithelialized and open.

Wounds assigned to the investigational treatment received the CCS for coverage. The outer dressing layers over the CCS test site remained undisturbed during the initial 72-hour postoperative period. On the third post-operative day, the outer layers were taken down to allow inspection of the CCS backing surface overlying the treatment site. The backing material was left in place at this time and gentle normal saline irrigation of the area was permitted to remove any exudate or debris that was adherent to the backing material. Thereafter removal and replacement of the outer dressing wrap on the CCS was permitted every 48-72 hours until Day 7, at which time attempts were made to remove the backing to allow the first direct visual assessment of the donor treatment site.

12.2 ADVERSE EVENTS

12.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

Of the 82 patients enrolled in the study, 64 (78.0%) had at least one adverse event. Overall, most of the adverse events were mild to moderate in severity, however there were three fatalities that were not related to donor site treatment. Sepsis, multiple organ system failure and dyspnea were the events associated with fatal outcomes. Serious

adverse events without donor site involvement were reported by 23 (28%) of the patients. There were no serious adverse events involving the donor sites. There were 12 adverse events involving the CCS site and 13 adverse events involving the Biobrane-L site. All of the adverse events with donor site involvement were mild to moderate in severity.

12.2.2 DISPLAY OF ADVERSE EVENTS

Table 12.2.1 lists the adverse events without donor site involvement that had an incidence of ≥ 5.0 % in one or more severity categories. Table 12.2.2 lists the adverse events without donor site involvement that had an incidence of < 5.0% in all severity categories. Most of the adverse events were considered unlikely to be related to the study treatment. No severe, life threatening, or fatal adverse events occurred at an incidence of ≥ 5.0%.

Table 12.2.1: Adverse Events with an Incidence ≥ 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System Preferred Term	n	%	n	%	n	%
Body As A Whole - General Disorders						
Fever	8	9.8	0		0	
Gastro-Intestinal System Disorders						
Constipation	16	19.5	0		0	
Nausea	8	9.8	1	1.2	0	
Vomiting	9	11.0	1	1.2	0	
Metabolic And Nutritional Disorders						
Hyperglycaemia	5	6.1	1	1.2	0	
Hypernatraemia	5	6.1	0		0	
Platelet,Bleeding & Clotting Disorders						
Thrombocythaemia	5	6.1	0		0	
Psychiatric Disorders						
Agitation	6	7.3	0		0	
Anxiety	5	6.1	0		0	
Insomnia	12	14.6	0		0	
Red Blood Cell Disorders						
Anaemia	11	13.4	1	1.2	0	
Reproductive Disorders, Female (N=19)						
Vaginal Haemorrhage (N=19)	1	5.3	0		0	
Respiratory System Disorders						
Atelectasis	5	6.1	0		0	
Pharyngitis	8	9.8	0		0	

Table 12.2.1: Adverse Events with an Incidence ≥ 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System Preferred Term	n	%	n	%	n	%
Skin And Appendages Disorders Pruritus	8	9.8	0		0	
Body System Unclassified Relaxation Of Scar	5	6.1	0		0	

Source: Section 14 Tables S10-A and S10-B

Table 12.2.2: Adverse Events with an Incidence < 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System/Preferred Term	n	%	n	%	n	%
Application Site Disorders						
Cellulitis	1	1.2	0		0	
Autonomic Nervous System Disorders						
Hypertension	1	1.2	0		0	
Hypertension Aggravated	1	1.2	0		0	
Hypotension	0	0.0	0		1	1.2
Sweating Increased	1	1.2	0		0	
Tachycardia	1	1.2	0		0	
Tachycardia Ventricular	1	1.2	0		0	
Body As A Whole - General Disorders						
Abdominal Pain	1	1.2	0		0	
Crying Abnormal	1	1.2	0		0	
Hypothermia	1	1.2	1	1.2	0	
Multiple Organ Failure	0	0.0	0		1	1.2
Oedema	3	3.7	0		0	
Pain	2	2.4	0		0	
Scar	2	2.4	1	1.2	0	
Cardiovascular Disorders, General						
Hypertension	1	1.2	0		0	
Hypertension Aggravated	1	1.2	0		0	
Hypotension	2	2.4	0		0	
Centr & Periph Nervous System Disorders						
Brain Stem Disorder	2	2.4	0		0	
Convulsions	2	2.4	0		0	
Dizziness	2	2.4	0		0	
Dysphonia	1	1.2	0		0	
Headache	2	2.4	0		0	

Table 12.2.2: Adverse Events with an Incidence < 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System/Preferred Term	n	%	n	%	n	%
Hyperreflexia	1	1.2	0		0	
Hypoaesthesia	1	1.2	0		0	
Muscle Contractions Involuntary	1	1.2	0		0	
Neuropathy	1	1.2	0		0	
Neuropathy Peripheral	1	1.2	0		0	
Paralysis	1	1.2	0		0	
Stupor	1	1.2	0		0	
Collagen Disorders						
Collagenosis	1	1.2	0		0	
Gastro-Intestinal System Disorders						
Achalasia Cardiae	0	0.0	1	1.2	0	
Anorexia	2	2.4	0		0	
Diarrhoea	4	4.9	0		0	
Dyspepsia	4	4.9	0		0	
Dysphagia	1	1.2	0		0	
Tooth Ache	1	1.2	0		0	
Heart Rate And Rhythm Disorders						
Cardiac Arrest	0	0.0	0		1	1.2
Fibrillation Ventricular	1	1.2	0		0	
Metabolic And Nutritional Disorders						
A/G Ratio Abnormal	1	1.2	0		0	
Dehydration	1	1.2	0		0	
Gout	1	1.2	0		0	
Hyperchloraemia	2	2.4	0		0	
Hyperkalaemia	2	2.4	0		0	
Hyperlipaemia	1	1.2	0		0	
Hypermagnesaemia	1	1.2	0		0	
etab/Nutritional Disord (continued)						
Hyperphosphataemia	1	1.2	0		0	
Hypocalcaemia	1	1.2	0		0	
Hypochloraemia	1	1.2	0		0	
Hypoglycaemia	1	1.2	0		0	
Hypokalaemia	3	3.7	0		0	
Hypophosphataemia	1	1.2	0		0	
Musculo-Skeletal System Disorders						
Back Pain	1	1.2	0		0	
Bone Development Abnormal	2	2.4	0		0	
Dystonia	0	0.0	1	1.2	0	
Myalgia	1	1.2	0		0	
Myo Endo Pericardial & Valve Disorders						

Table 12.2.2: Adverse Events with an Incidence < 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System/Preferred Term	n	%	n	%	n	%
Mitral Insufficiency	1	1.2	0		0	
Neoplasm						
Neoplasm Nos	1	1.2	0		0	
Platelet,Bleeding & Clotting Disorders						
Thrombocytopenia	3	3.7	0		0	
Thrombophlebitis Deep	1	1.2	0		0	
Psychiatric Disorders						
Confusion	2	2.4	0		0	
Depression	3	3.7	0		0	
Red Blood Cell Disorders						
Bilirubinaemia	2	2.4	0		0	
Reproductive Disorders, Male (n=63)						
Hernia Inguinal (n=63)	1	1.6	0		0	
Resistance Mechanism Disorders						
Healing Impaired	2	2.4	0		0	
Infection	4	4.9	0		0	
Infection Aggravated	1	1.2	0		0	
Pneumonia	1	1.2	0		0	
Sepsis	2	2.4	1	1.2	2	2.4
Respiratory System Disorders						
Aspiration	1	1.2	0		0	
Coughing	1	1.2	0		0	
Dyspnoea	0	0.0	3	3.7	1	1.2
Haemoptysis	1	1.2	0		0	
spiratory System Disorders (continued)						
Hypoxia	1	1.2	0		0	
Larynx Oedema	0	0.0	0		1	1.2
Pleural Effusion	2	2.4	0		0	
Pneumonia	0	0.0	1	1.2	0	
Pneumothorax	2	2.4	0		0	
Pulmonary Collapse	1	1.2	0		0	
Pulmonary Congestion	2	2.4	0		0	
Pulmonary Infiltration	3	3.7	0		0	
Pulmonary Oedema	1	1.2	0		0	
Respiratory Insufficiency	1	1.2	0		0	
Sinusitis	2	2.4	0		0	
Stridor	1	1.2	0		0	
Secondary Terms						
Ectropion	1	1.2	0		0	
Medication Error	1	1.2	0		0	

Table 12.2.2: Adverse Events with an Incidence < 5.0% by Severity

	Mild to Moderate N=82		Severe N=82		Life Threatening / Fatal N=82	
Body System/Preferred Term	n	%	n	%	n	%
Surgical Intervention	2	2.4	0		0	
Skin And Appendages Disorders						
Dermatitis Fungal	1	1.2	0		0	
Rash	1	1.2	0		0	
Skin Malformation	2	2.4	1	1.2	0	
Urinary System Disorders						
Dysuria	1	1.2	0		0	
Renal Failure Acute	1	1.2	0		0	
Urinary Retention	1	1.2	0		0	
Urinary Tract Infection	2	2.4	0		0	
Vascular (Extracardiac) Disorders						
Haematoma	1	1.2	0		0	
Haemorrhoids	1	1.2	0		0	
Vascular Disorder	2	2.4	0		0	
Vein Disorder	1	1.2	0		0	
Vision Disorders						
Eye Abnormality	1	1.2	0		0	
White Cell And Res Disorders						
Leucopenia	1	1.2	0		0	
Leukocytosis	2	2.4	0		0	
Lymphoedema	1	1.2	0		0	
Body System Unclassified						
Entropion/Ectrop Rep Nec	0	0.0	1	1.2	0	
Ext Fix Dev-Metacar/Carp	1	1.2	0		0	
Finger Amputation	2	2.4	0		0	
Full-Thick Skin Graft Nec	1	1.2	0		0	
Heterograft To Skin	1	1.2	0		0	
Lid Reconst W Skin Graft	1	1.2	0		0	
Lid Reconstr W Graft Nec	1	1.2	0		0	
Other Local Destruc Skin	3	3.7	0		0	
Other Pleural Incision	0	0.0	1	1.2	0	
Rehabilitation Nec	3	3.7	1	1.2	0	
Remove Impltd Device Nos	1	1.2	0		0	
Rotator Cuff Repair	1	1.2	0		0	
Skin Repair & Plasty Nec	2	2.4	0		0	
Skin Suture Nec	2	2.4	0		0	
Tot Nasal Reconstruction	1	1.2	0		0	

Source: Section 14 Tables S10-A and S10-B

There were 12 mild to moderate adverse events involving the CCS treated donor sites and 13 mild to moderate adverse events involving the Biobrane-L treated donor sites. The events for each treatment, the severity of the event and its frequency are presented in Table 12.2.3

Table12.2.3: Adverse Events With Donor Site Involvement

Adverse Event	CCS (n=82)				Biobrane-L (n=82)			
	Mild		Moderate		Mild		Moderate	
	n	%	n	%	n	%	n	%
Application site reaction	1	1.2	0		1	1.2	0	
Pain	2	2.4	2	2.4	2	2.4	2	2.4
Infection	1	1.2	0		1	1.2	0	
Surgical Site Reaction	1	1.2	0		1	1.2	0	
Bullous Eruption	0		0		1	1.2	0	
Pruritus	2	2.4	2	2.4	2	2.4	3	3.7
Rash Pustular	1	1.2	0		0		0	

Source: Section 16.10, Listing 30

12.2.3 ANALYSIS OF ADVERSE EVENTS

Most of the adverse events reported in this study were mild to moderate in severity and not associated with the donor site. The most frequent adverse events (i.e., ≥5.0%) were constipation (19.5%), insomnia (14.6%), anemia (13.4%), vomiting (11.0%), fever (9.8%), nausea (9.8%), pharyngitis (9.8%), pruritus (9.8%), agitation (7.3%), hyperglycemia (6.1%), hypernatremia (6.1%), thrombocythemia (6.1%), anxiety (6.1%), atelectasis (6.1%), relaxation of scar (6.1%), and vaginal hemorrhage in females (5.3%). All adverse events occurring at a frequency of ≥ 5.0% were mild to moderate in severity.

Both donor site treatments were well tolerated. There were no serious adverse events associated with the donor sites. Of the adverse events reported for the donor site, all were mild to moderate in severity. There were 12 adverse events associated with the CCS donor site and 13 associated with the Biobrane-L donor site, however all events

associated with CCS sites were judged to be unrelated to treatment. One event of pruritus at a Biobrane-L site was judged likely to be related to treatment.

12.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

Listing 30 in Appendix 16.10 shows all adverse events for each patient.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS.

12.3.1 DEATHS

Three patients died during the study. None of the deaths were considered related to the study treatment. Narratives describing the events experienced by the patients that died are provided in Section 12.3.3.

12.3.2 OTHER SERIOUS ADVERSE EVENTS

Table 12.3.1 summarizes the serious adverse events reported during the study. The total number of subjects reporting one or more serious adverse events was 24. All of the serious adverse events were considered unlikely to be related to study treatment. There were no serious adverse events involving the donor sites.

Table 12.3.1: Serious Adverse Events

Body System **Preferred Term**	**n**	**%**
Application Site Disorders		
Cellulitis	1	1.2
Autonomic Nervous System Disorders		
Hypotension	1	1.2
Body As A Whole - General Disorders		
Multiple Organ Failure	1	1.2
Scar	3	3.7
Centr & Periph Nervous System Disorders		
Brain Stem Disorder	1	1.2
Convulsions	1	1.2
Neuropathy	1	1.2
Gastro-Intestinal System Disorders		

Table 12.3.1: Serious Adverse Events

Body System Preferred Term	n	%
Achalasia Cardiae	1	1.2
Heart Rate And Rhythm Disorders		
Cardiac Arrest	1	1.2
Musculo-Skeletal System Disorders		
Bone Development Abnormal	1	1.2
Red Blood Cell Disorders		
Anaemia	1	1.2
Resistance Mechanism Disorders		
Healing Impaired	2	2.4
Infection Aggravated	1	1.2
Sepsis	3	3.7
Respiratory System Disorders		
Dyspnoea	4	4.9
Larynx Oedema	1	1.2
Pneumonia	1	1.2
Pneumothorax	1	1.2
Secondary Terms		
Ectropion	1	1.2
Skin And Appendages Disorders		
Skin Malformation	3	3.7
Urinary System Disorders		
Renal Failure Acute	1	1.2
Vascular (Extracardiac) Disorders		
Haematoma	1	1.2
White Cell And Res Disorders		
Lymphoedema	1	1.2
Body System Uncategorized		
Entropion/Ectrop Rep Nec	1	1.2
Lid Reconst W Skin Graft	1	1.2
Lid Reconstr W Graft Nec	1	1.2
Tot Nasal Reconstruction	1	1.2
Other Pleural Incision	1	1.2
Ext Fix Dev-Metacar/Carp	1	1.2
Remove Impltd Device Nos	1	1.2
Rotator Cuff Repair	1	1.2
Finger Amputation	1	1.2
Other Local Destruc Skin	3	3.7
Skin Suture Nec	2	2.4
Full-Thick Skin Graft Nec	1	1.2
Heterograft To Skin	1	1.2
Relaxation of Scar	4	4.9
Skin Repair & Plastic NEC	2	2.4
Rehabilitation NEC	1	1.2

Table 12.3.1: Serious Adverse Events

Body System Preferred Term	n	%

urce: Section 14, Tables S6-A and S6-B

12.3.3 NARRATIVES OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

12.3.3.1 Deaths

Patient 01-008

Patient 01-008, a 42-year old male experienced multiple adverse events. His relevant medical history includes a 43% total body surface area burn injury, septic shock and gram-negative septicemia with E. coli organisms. Antibiotic therapy was adjusted and continued. On June 1, 1999 he underwent excision and grafting of the burn injury, at which time the investigational device was placed on the donor sites. On the day of surgery, the patient became hemodynamically unstable and required support with appropriate pressors. He also developed adult respiratory distress syndrome (ARDS) and ventilator changes were made. On June 2, 1999, the patient was documented as having non-oliguric renal failure and drug therapy was initiated. On June 6, 1999, the patient remained critically ill but was post-E. coli septic shock. On June 14, 1999, the condition worsened and the patient required hemodialysis. The patient was noted to have a worsening right side pneumothorax and required a chest tube to reinflate the lung. Patient remained stable before and after the insertion of the chest tube. On June 16, 1999 symptoms were resolving but ARDS continued.

On June 24, 1999, the patient died due to multi-system organ failure. At the time of death, the patient had grown more hemodynamically unstable and experienced full cardio-pulmonary arrest the morning of his death. Over the ten days prior to his death, the patient's condition had declined due to multi-system organ failure from burn wound septic shock mediated initially by E. coli and subsequently complicated by a wound

fungemia. These serious adverse events were judged to be unrelated to the investigational device (CCS) by both the Investigator and the Ortec Medical Director.

Patient 15-007

Patient 15-007, a 76-year-old female developed respiratory distress evidenced by shortness of breath. The event, which occurred on March 1, 2000, was considered severe. The patient was subsequently intubated to secure her airway and prevent respiratory failure. Her relevant medical history includes a 15% TBSA burn injury as well as excision and grafting on February 23, 2000 at which time the investigational device was placed on the donor sites. She then developed bacterial sepsis, which was considered fatal on March 10, 2000. Her condition began to deteriorate as evidenced by hypotension, and decreasing urine output. Upon family request, all aggressive supportive measures were terminated. These adverse events were considered by the Investigator to be unlikely related to the study device (CCS). The adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 15-009

Patient 15-009, a 37-year-old female suffered a cardiac arrest, on March 10, 2000, which was considered life threatening. She was successfully resuscitated and upon family request, all medications were discontinued and she was placed on minimal ventilator settings. She also suffered acute respiratory distress syndrome (ARDS) which was considered fatal. Her relevant medical history includes 65% TBSA burn injury as well as excision and grafting on March 3, 2000 at which time the investigational device was placed on the donor sites. Her death is attributed to complications from her burn injury and was considered by the Investigator unlikely to be related to the study device (CCS). Ortec's Medical Director reviewed the adverse events and determined that they were unrelated to the study device.

12.3.3.2 Other serious adverse events

Patient 01-005

Patient 01-005, a 39-year-old male was hospitalized for several corrective surgical procedures to repair extensive burn and scar deformities. The events were considered mild in severity and began on October 5 lasting through December 21, 1999. The procedures included contracture releases, complex closure of a wound dehiscence, placement of PICC catheter, K-wire fixation and subsequent removal of K-wires, and grafting, removal of Steinmann pin from hand, and facial reconstruction. His relevant medical history included a 32% TBSA thermal burn injury resulting in severe burn scars and contractures as well as excision and grafting on May 18,1999 at which time the Investigational device was placed on the donor sites. These surgical procedures are considered by both the Investigator and Ortec's Medical Director to be unrelated to the investigational device, (CCS). Subsequently, he was readmitted to the hospital to evaluate an ectropion of the right eye. The event which began on March 31,2000 was considered moderate in severity. The patient was taken to the OR for evaluation under anesthesia and possible attempt at repair. The patient was discharged on April 3, 2000. This event was considered by both the Investigator and Ortec's Medical Director unlikely to be related to the study treatment. This hospital readmission was considered by the Investigator to be unlikely related to the study device (CCS). This hospital admission was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 01-007

Patient 01-007, a 7- year old female, was admitted to the hospital for release of a contracture involving the left popliteal fossa and excision of a chronic wound. The event which began on May 1,2000 was considered mild in severity. Her relevant medical history included a 33% TBSA burn injury as well as excision and grafting on May 1999, at which time the investigational device was placed on the donor sites. This adverse event was considered by both the Investigator and Ortec's Medical Director unlikely to be related to the study device (CCS). The patient was subsequently re admitted to the

hospital for reconstructive surgery of burn scars on bilateral thighs. The event, which began on September 7, 2000, was considered mild in severity. Her relevant medical history included a 33% TBSA burn injury as well as excision and grafting in June 1999 at which time the investigational device was placed on the donor sites. This event was considered by the Investigator unlikely to be related to the study device. Ortec's Medical Director reviewed the events and determined that they were unrelated to the investigational device.

Patient 01-009

Patient 01-009, a 35-year-old male, was re-admitted to the hospital with a diagnosis of a contracture of the left axilla and median nerve entrapment. The event, which began on June 20, 2000, was considered mild in severity. His relevant medical history included a 65% TBSA burn injury as well as excision and grafting in August 2000, at which time the investigational device was placed on the donor sites. This adverse event was considered by the Investigator as unlikely to be related to the study device (CCS). This adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the investigational device.

Patient 01-012

Patient 01-012 a 61-year old female experienced an adverse event that consisted of the development of a new right occipital lobe infarction, identified by CT scan. She was placed on one-half aspirin per day and further evaluation was sought via a carotid doppler exam. The doppler results were unremarkable; there was no evidence of atherosclerotic disease, no hemodynamically significant stenosis, and no significant surface irregularities. Her relevant history included a head injury with loss of consciousness, respiratory arrest requiring intubation, a previous right frontal region brain infarction and a 22 % TBSA burn injury as well as excision and grafting on August 16, 1999 at which time the investigational device was placed on the donor sites. This serious adverse event

was judged to be unrelated to the investigational device (CCS) by both the Investigator and Ortec's Medical Director.

Patient 01-016

Patient 01-016, a 26-year-old male was admitted to the hospital for the surgical treatment of a non-healing wound of the lower left extremity. The event took place on January 3, 2000. He was treated surgically with a commercially available biological dressing, Apligraf®. The patient did well and was discharged on January 6, 2000. His relevant medical history included a 50% TBSA burn injury as well as excision and grafting on September 27, 1999 at which time the investigational device was used to treat the donor sites. This adverse event was considered by the Investigator and Ortec's Medical Director to be unrelated to the study device (CCS).

Patient 01-017

Patient 01-017, a 75-year-old male was admitted to the hospital for release of a contracture of the right axilla. The event, which occurred on March 30, 2000, was considered mild in severity. His relevant medical history included a 20% TBSA burn injury as well as excision and grafting in September 1999 at which time the investigational device was placed on the donor sites. This adverse event was considered by the Investigator and Ortec's Medical Director unlikely related to the study device (CCS).

Patient 01-018

Patient 01-018, a 64-year old male, was hospitalized for swelling of his left arm to rule out cellulitis or lymphedema. The event occurred on November 30, 1999 and was considered moderate in severity. The patient was diagnosed with lymphedema. The patient was treated and the problem resolved. The patient's relevant history included an escharotomy of the left medial forearm and a 22% TBSA burn injury as well as excision and grafting at which time the investigational device was placed on the donor sites. This

serious adverse event was judged to be unrelated to the investigational device (CCS) by both the Investigator and Ortec's Medical Director.

Patient 03-001

Patient 03-001, a 39-year-old male, was admitted to the hospital for left elbow contracture release and heterotopic ossification excision. The event, which occurred on April 11, 2000, was considered moderate in severity. His relevant medical history included a 85% TBSA burn injury as well as excision and grafting on July 21, 1999, at which time the investigational device was placed on the donor sites. This adverse event was considered by both the Investigator and Ortec's Medical Director unlikely to be related to the study device (CCS). He had previously been admitted to a facility for rehabilitation purposes on November 16, 1999, due to the extensive size of the previous burn injury. The event was considered moderate in severity and unrelated to the investigational device (CCS). On June 18, 2000 he had another hospital admission for moderately severe cellulitis of his left arm. That event was also considered unlikely to be related to the investigational device.

Patient 03-005

Patient 03-005, 40- year old male, was admitted to the hospital for outpatient surgery for excision of a hypertrophic right hand and index scar with a split thickness skin graft placement. The event which occurred on May 24, 2000 was considered mild in severity. His relevant medical history included a 30% TBSA burn injury as well as excision and grafting on September 3, 1999 at which time the investigational device was placed on the donor sites. This adverse event was considered by both the Investigator and Ortec's Medical Director unlikely related to the study device (CCS).

Patient 03-006

Patient 03-006, a 38- year old male, was admitted to the hospital for outpatient surgery to release a burn scar contracture of his left groin. The event, which occurred on August 16,

2000, was considered mild in severity. His relevant medical history included a 55 % TBSA burn injury as well as excision and grafting on October 6, 1999 at which time the investigational device was placed on the donor sites. This adverse event was considered by both the Investigatorand Ortec's Medical Director unlikely to be related to the study device (CCS).

Patient 03-007

Patient 03-007, a 64-year-old male, was admitted to rehabilitation facility due to the size of the previous burn injury. The event, which occurred on February 18, 2000, was considered severe. The patient was subsequently discharged on February 25, 2000 because of his improved condition. However because of worsening dysphagia he experienced aspiration pneumonia, which was considered severe. He also required treatment for a urinary tract infection. He received medical treatment and was discharged home and was then readmitted on March 30, 2000 to undergo left thoracotomy with Heller myomotomy to relieve symptoms of severe dysphagia. His relevant medical history included a 40% TBSA of second and third degree burns, peptic ulcer disease (PUD), dysphagia, as well as excision and grafting on January 19, 2000 at which time the investigational device was placed on the donor sites. All of the adverse events and hospital admissions were considered by the Investigator and Ortec's Medical Director as unlikely to be related to the investigational device (CCS).

Patient 03-009

Patient 03-009, a 40-year-old male, was admitted to a rehabilitation hospital for aggressive physical therapy. The event, which occurred on August 4, 2000, was considered moderate in severity. His relevant medical history included a 65% TBSA burn injury as well as excision and grafting on May 10, 2000 at which time the investigational device was placed on the donor sites. This adverse event was considered by both the investigator and Ortec's Medical Director as unlikely to be related to the investigational device (CCS).

Patient 04-001

Patient 04-001 a 23-month-old male experienced hypotension post operatively and required dopamine treatment. A septic episode was suspected. The patient's white blood cell count was 25.1, with a fever of 37.0 Celsius. His relevant history included a 65% TBSA burn injury as well as excision and grafting on June 25, 1999 at which time the investigational device was placed on the donor sites. This adverse event was judged by the Investigator to be unlikely related to the study device (CCS). The adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 04-009

Patient 04-009, a 6 year old male, had amputation of the fingers due to burn injury during initial hospitalization was re- admitted to the hospital for excision of scalp wound, contracture releases of face and left hand and nasal reconstruction, which were all considered moderate in severity between February 4, 2000 to November 8, 2000. His relevant medical history included a 26% TBSA burn injury as well as excision and grafting on October 8, 1999 at which time the investigational device was placed on the donor sites. The adverse events were considered by the Investigator to be unlikely related to the study device (CCS). The adverse events were reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 04-014

Patient 04-014, a 14-year-old female was re- admitted to the hospital for increased seizure activity. The event occurred on July 13, 2000 and was considered mild in severity. The EEG did not capture any seizure activity and the patient was discharged home two days later. Her relevant history included a seizure disorder diagnosed in February 2000, and a 20 % TBSA burn injury as well as excision and grafting on April 12, 2000 at which time the investigational device was placed on the donor sites. This adverse event was judged by the Investigator to be unlikely related to the study device

(CCS). The adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 05-001

Patient 05-001, a 29-year-old male, was re-admitted to the hospital for intermittent surgeries for hypertrophic scarring. The re-admisssions occurred during the period of December 6, 1999 through September 14, 2000 and were considered severe. His relevant medical history included a 37% TBSA burn injury as well as excision and grafting on July 16, 1999 at which time the investigational device was placed on the donor sites. The readmissions were considered by the Investigator to be unlikely related to the study device (CCS). The readmissions to the hospital were reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 05-002

Patient 05-002, a 59-year-old male, was re-admitted to the hospital for release of left arm contracture and hypertrophic scarring with corticosteriod injections. The events occurred on December 13, 1999 and were considered moderate in severity. His relevant medical history included a 25% TBSA burn injury as well as excision and grafting on July 28, 1999 at which time the investigational device was placed on the donor sites. These adverse events were considered by the investigator to be unlikely related to the study device (CCS). The adverse events were reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 08-001

Patient 08-001 was admitted to the hospital for repair of a right rotator cuff as well as facial reconstruction of the right lower eyelid, right cheek and reconstruction of the elbow. The events occurred during the period of July 6, 1999 through July 8, 1999 and were considered mild in severity. His past relevant history included epilepsy and a 20%

TBSA burn injury as well as excision and grafting on May 25, 1999 at which time the investigational device was placed on the donor sites.

He was subsequently readmitted to the hospital at two separate intervals for primary stage facial reconstruction related to burn injuries. The first admission occurred on September 13th, 1999 and was considered mild in severity. The patient was discharged on September 14th, 1999. The second admission occurred on October 4th, 1999 for facial reconstruction related to burn injuries and was considered mild in severity. The patient was subsequently discharged on October 8, 1999.

Another readmission to the hospital was required on October 27, 1999 for evacuation of a hematoma involving the neck and cervicofacial flap which had developed three weeks after undergoing facial reconstruction. The hematoma occurred in the operative region. The event was considered moderate in severity. The patient was subsequently discharged. All of the adverse events experienced by this patient were judged to be unlikely related to the investigational device (CCS) by the Investigator. The adverse events were reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 15-001

Patient 15-001, a 33-year-old male, was re-admitted to the hospital to undergo repair of a right ectropion with a full thickness skin graft to the right lower eyelid. The event, which occurred on March 2, 2000, was considered severe. His relevant medical history included a 35% TBSA burn injury as well as excision and grafting on November 24, 1999 at which time the investigational device was placed on the donor sites. The adverse event was considered by the Investigator to be unlikely related to the study device (CCS). The adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

Patient 15-005

Patient 15-005, a 35-year-old female was re-admitted to the hospital for a local wound infection. The event occurred on March 8, 2000 and was considered moderate in severity. Her relevant medical history included a 28% TBSA burn injury as well as excision and grafting on February 11, 2000 at which time the investigational device was placed on the donor sites. The adverse event occurred during a follow-up visit and was considered by the Investigator to be unlikely related to the study device (CCS). The adverse event was reviewed by Ortec's Medical Director and determined to unrelated to the study device.

Patient 15-010

Patient 15-010, a 32-year-old male, was re-admitted to the hospital for right hand contractures resulting in limited range of motion and decreased sensation. The event occurred on June 28, 2000 and was considered severe. His relevant medical history included a 15% TBSA burn injury as well as excision and grafting on March 26, 2000 at which time the investigational device was placed on the donor sites. This adverse event was considered by the Investigator to be unlikely related to the study device (CCS). The adverse event was reviewed by Ortec's Medical Director and determined to be unrelated to the study device.

12.3.4 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events.

In this study of patients with burn injuries, the incidence of adverse events was 78%. This is not unexpected considering the morbidity and mortality that can be associated with burns. There were three deaths among the study subjects. All of the deaths occurred in subjects who were elderly or who had burn injuries involving >40% TBSA. The causes of death were sepsis, septic shock with multiple organ failure and respiratory failure that were complications of the burn injury. None of the deaths were related to the investigational device, CCS. Twenty-eight percent of the study population experienced

serious adverse events, which were most likely consequences of underlying disease states. None of the serious adverse events were attributed to the use of CCS.

The majority of the adverse events experienced by the study participants were of mild to moderate severity and all were judged to be unrelated to CCS. Only one adverse event, pruritus at the Biobrane site, was judged to be likely related to the study. The most frequent adverse events (i.e., ≥5.0%) were constipation (19.5%), insomnia (14.6%), anemia (13.4%), vomiting (11.0%), fever (9.8%), nausea (9.8%), pharyngitis (9.8%), pruritus (9.8%), agitation (7.3%), hyperglycemia (6.1%), hypernatremia (6.1%), thrombocythemia (6.1%), anxiety (6.1%), atelectasis (6.1%), relaxation of scar (6.1%), and vaginal hemorrhage in females (5.3%). All adverse events occurring at a frequency of ≥ 5.0% were mild to moderate in severity.

Both donor site treatments were well tolerated. There were no serious adverse events associated with the donor sites. Of the adverse events reported for the donor sites, all were mild to moderate in severity. There were 12 adverse events associated with the CCS donor site and 13 associated with the Biobrane-L donor site.

12.4 CLINICAL LABORATORY EVALUATION

Not applicable

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

There were no clinically significant changes in mean body temperature or blood pressure (systolic and diastolic) throughout the 24 weeks of follow up. Pretreatment tachycardia was present (mean pulse rate 110). By the Day 28 visit, the mean pulse rate was 98. Summaries of body temperature, systolic blood pressure, diastolic blood pressure, pulse and weight are displayed in Section 14.3 Tables S17, S18, S19, S20, and S21, respectively.

Nutritional Evaluation

By day 28 of the study follow-up period, approximately 33% of patients were meeting or exceeding their required daily caloric intake, however, 25% of the study population had caloric intake values that indicated ongoing catabolism. There was not enough data to assess the caloric status of the rest of the study population. Patient listing of nutritional assessments by visit are contained in Section 16.10, Listing 28 and summarized in Section 14.3, Table S22.

Assay for Collagen Type I IgG Autoantibodies

Table 12.5.1 displays screening and week 24 results of testing for collagen Type I IgG autoantibodies. A listing of individual patient results may be found in Section 16.10, Listing 37.

Table 12.5.1: Summary of Collagen Type I IgG Autoantibodies

	Screening	Week 24	Difference Week 24 - Screening
N	79	54	53
Mean (SD)	8.3 (22.07)	10.5 (18.70)	1.5 (18.9)
Median	5	5	0
Min, Max	<5, >200	<5, 111	-89, 73

Source: Section 14, Table S2

The mean rise in collagen Type 1 autoantibodies over the 24 weeks after surgery was 1.5 (SD 18.9) with a median difference of zero. A total of 19 patients had elevated IgG at some point during the 24-week post surgical period. Of these 19 patients, nine demonstrated elevated levels at screening, indicating the elevated titer post surgery was probably not due to product. Three of the 19 patients had transient elevations that were totally or partially back to normal by week 24. An additional three patients who began with an elevated titer demonstrated lower levels upon subsequent testing. Leaving four patients with significantly increased anti Collagen I IgG titers that may have been attributed to the use of CCS. However, no patient with an elevated titer at any time was

found to have clinical evidence of graft rejection, and, in fact, the healing times in these patients were identical to those for the entire patient group. Given the high incidence of abnormal titers at time zero, a the similar incidence of rising and falling titers over time, and the lack of clinical signs and symptoms of graft rejection in any patient with elevated titers, a clinically meaningful association between the use of CCS and the inducement of anti-collagen I antibody cannot be concluded.

12.6 SAFETY CONCLUSIONS

Both donor site treatments were well tolerated. Of the donor site adverse events reported, all were mild to moderate in severity. There were no serious adverse events associated with the donor sites.

13. DISCUSSION AND OVERALL CONCLUSIONS

Harvesting split thickness skin grafts creates more open surface area (donor sites) for the already challenged burn patient thereby increasing their susceptibility to infections and metabolic complications. Optimizing the management of donor site wounds can produce substantial benefits by accelerating and preventing delays in wound healing, decreasing the incidence of local infection, reducing pain and discomfort at the donor site, improving cosmetic outcomes and reducing, or eliminating entirely, the costs that would be incurred for treatment of donor site wound complications.

Paying scrupulous attention to the care of the donor site wounds can also produce an extremely important clinical advantage in patients who have experienced massive surface area burns. Massive surface area injuries limit availability of viable donor sites. In an attempt to maximize the use of the patients' limited uninjured skin, fascial excision and meshing of donor skin to create a wide expansion are management strategies that a burn surgeon might employ. These procedures, however, render the patient susceptible to wound contractures and hypertrophic scar formation leaving them burdened with severe long-term functional and cosmetic sequelae that impede their resumption of activities of

daily living. An alternative option involves reharvesting of previously used donor sites (i.e., "recropping"). However, there is a waiting period during which maturation of donor site has to occur so as to yield a viable conventional split thickness skin graft which functions effectively in facilitating wound closure. Optimizing donor site wound management can promote accelerated healing and lead to the earlier availability of new skin that can be recropped.

This study was a prospective, controlled, randomized, multicenter study designed to examine the safety and efficacy of CCS in facilitating timely wound closure of split thickness skin donor sites in burn patients, compared to a standard care dressing, Biobrane-L. The study had a matched-pairs design and enrolled patients who required conventional split thickness skin autografting for the management of burn injuries.

Results obtained from this study clearly demonstrate the superiority of CCS over Biobrane-L in time to complete wound closure, percentage of donor sites healed by day 32, rate of wound closure, time to readiness for re-cropping, and scarring severity. Furthermore, a clinically meaningful difference was noted, in favor of CCS, for rate of infection, donor site breakdown, and pain.

The primary efficacy outcome variable (i.e., time to complete wound closure) was measured by three separate methods, photography, planimetry, and investigator assessments. All assessment methods provided clinically meaningful and statistically significant results ($p<0.05$) demonstrating the superiority of CCS over a conventional treatment for skin graft donor sites. By photographic assessment, complete wound closure with CCS occurred 7 days earlier than with Biobrane-L. By planimetry, complete wound closure with CCS occurred 5 days earlier. Investigator assessment indicated that complete wound closure with CCS occurred 4 days earlier than with Biobrane-L. Additionally, the statistically significantly ($p<0.05$) shorter time to complete wound closure with CCS was consistent across the ITT and Per Protocol populations and persisted regardless of age, race, gender, size of donor site, or percentage of total body surface area burned.

The percentage of CCS donor sites completely healed by day 32 was also statistically significantly higher than that of Biobrane-L with all three assessment methods. By photographic assessment, 24% more CCS donor sites were healed than Biobrane-L (p=<0.0000). By planimetry, CCS healed sites were 12% higher (p=0.0039); and by investigator assessment, CCS healed sites were nearly 10% higher (p=0.0047).

The accelerated time to 100% wound closure with CCS versus Biobrane-L is clearly reflected in the daily rate of wound closure. Planimetry data from this study indicate that during the first 16 days of treatment, CCS treated sites healed at a mean rate of 6.3 cm^2/day while Biobrane-L treated sites healed at a mean rate of 3.8 cm^2/day, demonstrating a statistically significant difference that translates into a CCS healing rate that is nearly 70% faster than Biobrane-L during the first 16 days of therapy. The rates of wound closure for both CCS and Biobrane-L appear to decrease after the 16^{th} day, however, the mean rate of wound closure for CCS during this time period remained greater than that of Biobrane-L by 16% (i.e., approximately 4.0 cm^2/day and 3.5 cm^2/day, respectively).

Wound measurement and determination of wound healing are matters of significant controversy in published reports. Most published studies are single site studies and the assessment of 100% wound closure varies as well. In some studies 95% or 98% wound closure is considered as completely healed; in some studies complete reepithelialization is considered as complete healing; and in other studies the patients are only followed until day 14 and the percentage of wound closure is recorded at that time. Most studies also rely on only one evaluation method, usually the investigator's visual assessment.

Among the three methods used in this study (i.e., investigator's clinical assessment, planimetry and photography), photography is the most objective method, however it is less accurate and sensitive than planimetry and the investigator's clinical assessment. The objectivity of the photographic method is based on blinded expert reviewers who are totally unconnected to the study. This method, however, is not as accurate or sensitive as planimetry or the investigator's clinical assessment due to confounding factors such as

the possibility of inconsistent lighting, limitation to viewing the wound in one direction, and the inability to touch the wound. Additionally, there is no interactivity with the patient when using photography. Planimetry depends upon the clinician's judgment of the wound edges, and uses computerized tools to calculate wound area. Because the clinician is able to view the wound from multiple directions, to touch the wound and to question the patient about pain in different sites, the resulting wound tracing is inherently more accurate than using photography. However, when the wound is completely resurfaced with thin epithelium, photography might not indicate 100% healing, only physical examination can determine if the reepithelialization is truly complete. Detecting continued wound drainage on physical examination, for example, suggests the presence of microscopic skin defects not demonstrable on photography or planimetry. These considerations notwithstanding, the present study demonstrates similar results when assessed by all three methods.

A number of factors have been associated with time to complete wound healing. Wound healing can be delayed in patients with extensive burns, advanced age, or deeper wounds. In one study comparing hydrophilic polyurethane to petrolatum gauze, where the mean donor site surface areas were 89.2 cm^2 and 77.6 cm^2 respectively, and the mean age of patients was 62.8 years, the number of days to complete reepithelialization was 20.6 days for hydrophilic polyurethane and 19.3 days for petrolatum gauze.[12] In a younger patient population utilizing Biobrane as the dressing, healing times have been as short as 9.7 days in a pediatric population with a mean age of 7.9 years[13] compared to a mean of 19 days in another study where the mean age of patients receiving the Biobrane treatment was 51 years.[14]

In the present study, the patient population was acutely catabolic, as evidenced by a baseline daily caloric intake of 2384 calories and mean albumin of 2.0 grams/dL. The mean age for the patients in this study was 31.7 years and the mean donor site surface area was 94.4 cm^2 for CCS treated wounds and 94.3 cm^2 for donor site wounds treated with Biobrane-L.

Patients with a larger percentage of total body surface area burned also heal more slowly. Zapata-Sirvent et al.[15] reported a mean healing time of 9.8 days for Biobrane in a population of 31 patients with a mean TBSA burn injury of 11.5%. In a second study by Hansbrough,[9] where the mean TBSA burn injury was higher (26%), the mean time to Biobrane removal was 13.3 days.

In the current study, no patients were enrolled with burns under 10% of TBSA. The mean percentage of TBSA burned was 29.5% and the mean healing time for Biobrane-L ranged from 18 to 22 days, depending on the assessment methodology (i.e. photography, planimetry or investigator evaluation). The extended healing time for Biobrane-L compared to healing times previously reported in the literature is a function of the increased mean percentage of TBSA burned, and other factors, in this population of seriously ill patients.

A subset analysis of percent TBSA burned in the current study population, confirmed that prolongation of healing time is directly correlated with more extensive TBSA burn injuries. When TBSA burned was 10-20%, mean healing times (±SD) by planimetric analysis were 11.8±3.0 and 13.6±4.2 days for CCS and Biobrane-L, respectively. When TBSA burned was between 21 and 40%, the mean healing times were extended to 14.1±6.9 days for CCS and 20.6±8.9 days for Biobrane-L. In the group with the most extensive TBSA burn injuries (i.e., greater than 40%), the mean healing times were 15.4±4.5 days for CCS and 23.5±7.1 days for Biobrane-L.

Time to readiness for recropping was also used as a measure of efficacy. CCS treated sites were ready for recropping 7 days earlier (median value) than Biobrane-L treated donor sites. Mean time to readiness for recropping was 15.9 days for CCS treated sites and 20.8 days for Biobrane-L treated sites, ($p=0.0002$). The accelerated healing of the CCS sites relative to the Biobrane-L sites is clinically significant in that the CCS donor sites were able to provide a source of viable skin for autografting earlier than the Biobrane-L treated sites. The ability to recrop donor sites expediently hastens permanent coverage of injured body surface areas thus potentially reducing morbidity and mortality.

Since complete coverage of the burns must be achieved prior to hospital discharge, this would be expected to translate into earlier hospital discharge. Hospital discharge and economic data were not measured in this study. However, considering that much of the care of a seriously burned patient is conducted in the intensive care unit, reducing this stay by even a few days would translate into many thousands of dollars saved.

Although a large portion of the study population experienced adverse events, most of the adverse events were related to the underlying burn injury and all adverse events were judged to be unrelated to CCS. Since patients with burn injuries are very susceptible to infections and metabolic and dermatologic complications related to their injuries, the occurrence of a large number of adverse events, some of which were serious, was not unanticipated. Three patients died during the study however, none of the deaths were considered related to the study treatment. The most frequent adverse events were constipation, insomnia, anemia, nausea and vomiting.

It is noteworthy that there were no serious adverse events that were associated with the donor sites. All of the donor site adverse events were mild to moderate in severity and included pain, infection, application site reaction, surgical site reaction, bullous eruption and pruritus. There were 12 events associated with the CCS site and 13 events associated with the Biobrane-L site. The frequency and severity of pain, infection, application site reaction and surgical site reaction were exactly the same, 5%, 1%, 1%, and 1% respectively, for the CCS and Biobrane sites. Mild to moderate pruritus was reported for 6% of the Biobrane-L sites and 5% of CCS sites. The incidence of mild bullous eruption was 1% at the Biobrane-L sites and 0% at the CCS sites. Pustular rash was observed at 1% of CCS sites and 0% at Biobrane-L sites.

Both the Hamilton Scar Score and the Vancouver Scar Score values were significantly better (lower) for the CCS treated sites at Week 12 and Week 24. Clinically meaningful differences in signs of infection and breakdown were observed between CCS and Biobrane sites, in favor of CCS. Additionally, the average mean pain intensity during the

first 16 days after surgery was approximately 25% more at the Biobrane sites. CCS treated sites were significantly less painful on Days 9, 11, and 12 than Biobrane-L sites.

For the study population as a whole, there were no clinically significant changes in vital signs throughout the 24 weeks of follow-up. Pretreatment mean pulse rate was 110 beats per minute that gradually decreased and was below 100 beats per minute by the Day 28 study visit.

The CCS treated donor sites had a significantly raster rate of healing by each of the three assessments (photography, planimetry and investigator evaluation) employed. The faster healing of CCS treated sites resulted in earlier times to readiness for recropping for these sites relative to Biobrane-L treated sites and a significantly larger proportion of CCS sites achieved complete wound closure by day 32. Both donor site treatments were well tolerated with similar frequencies of mild to moderate donor site associated adverse events, however scar outcome was significantly better, as measured by both the Vancouver Scar Score and the Hamilton Scar Score, for CCS sites at weeks 12 and 24.

The results demonstrate that CCS was more effective in facilitating timely wound closure of split thickness skin donor sites in burn patients compared to Biobrane-L. Healing time for CCS treated donor sites was statistically significantly shorter than for the Biobrane-L product. This acceleration of wound healing is clinically important in enabling earlier recropping, alleviating donor site pain, reducing infection rates, and improving post-operative patient mobilization. These factors are also expected to result in earlier patient discharge when CCS is used.

In conclusion, treatment of donor site wounds with CCS is well-tolerated, promotes more rapid healing and has reduced scarring when compared to conventional therapy with Biobrane L®.